Epinephrine
Cardiovascular Emergencies Symposium 2018
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High Quality BLS
- Compress at 100-120/minute
- Compress 2 inches
- Allow full chest rise
- Minimize interruptions
- Do not hyperventilate (8-10/minute)

“High Quality” ACLS
- **Intubate Oxygenate and Hyperventilate**
  - Epinephrine 1 mg Q 3 minutes
  - Atropine 1 mg Q 3 minutes
  - Calcium Chloride 1 mg Q 3 minutes
  - Bicarbonate 2 amps IVP / 1 Q 5 min

Epinephrine Use
Standard dose epinephrine (1 mg Q 3-5 minutes) may be reasonable for patients with cardiac arrest (class 11b)
Epinephrine’s Pharmacologic Actions

- A potent alpha agonist
  - ↑ Peripheral resistance
  - ↑ End aortic diastolic pressure
  - ↑ Coronary and carotid blood flow

- A potent beta agonist
  - ↑ Myocardial contractility
  - ↑ Amplitude of fibrillatory wave
  - ↑ Oxygen consumption

Epinephrine is the ACLS drug that has “stood the test of time”

The two fathers of modern CPR
- Both anesthesiologists
- Baltimore City Hospital, Johns Hopkins, University of Maryland
- Used small dogs to evaluate drugs in CPR

Table 1.—Effect of Drug Therapy on Ventricular Defibrillation

<table>
<thead>
<tr>
<th>Group</th>
<th>Drug, Dose</th>
<th>Number Defibrillated</th>
<th>Number Counterchecks Required</th>
<th>Number With Return of Circulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>None</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>Sodium bicarbonate, 1.5 gm</td>
<td>6</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>C</td>
<td>Epinephrine, 1 mg</td>
<td>7</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>D</td>
<td>Epinephrine, 1 mg; lidocaine, 40 mg</td>
<td>13</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>E</td>
<td>Phenylephrine hydrochloride, 10 mg</td>
<td>12</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>F</td>
<td>Methoxamine hydrochloride, 20 mg</td>
<td>14</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>G</td>
<td>Epinephrine, 1 mg; sodium bicarbonate, 1.5 gm</td>
<td>13</td>
<td>7</td>
<td>6</td>
</tr>
</tbody>
</table>

JAMA 1968;203:93-98

Table 2.—Relation Between Drug Therapy and Survival

<table>
<thead>
<tr>
<th>Group</th>
<th>Drug, Dose</th>
<th>Circulation Restored</th>
<th>Condition in 24 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>None</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>Sodium bicarbonate, 1.5 gm</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
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<td>10</td>
</tr>
</tbody>
</table>
Compared early vs late epinephrine in Asystole
- 2 groups of 10 dogs using 1 mg of epinephrine
- Group 3 received epi after 1 min Asystole
- Group 4 received epi after 10 mins Asystole

Take Home #1

Early administration of epinephrine appears to be the optimal pharmacologic therapy in CPR based on its use in a relatively low number of small dogs

“I question the choice of epinephrine as the emergency drug to use in cardiac arrest”

Eastwood DW. Discussion of “Influence of peripheral vascular tone on cardiac resuscitation. Anesth Analg 1965;44:750

“Physicians should question the routine use of epinephrine in coarse ventricular fibrillation. In this situation a pure alpha antagonist, which does not have epinephrine’s adverse myocardial effects might be significantly more beneficial”

**Take Home #2**

Epinephrine’s effectiveness has been questioned for more than 50 years

If 1 mg of epinephrine is the right dose in 10 kg dogs, are larger doses more appropriate in 60-100 kg humans?

**High Dose Epinephrine**

• Higher doses of epinephrine are required to better improve and end aortic diastolic pressure
• 0.1 mg/kg not 0.01 mg/kg needed to adequately perfuse the head and the heart
• 1 mg in 10-20 kg dog = 5-10 mg in 50-100 kg adult
• There are now many subjective reports of success with “high dose” epinephrine

**High Dose Epinephrine “Right Dose” Epinephrine**

• Dramatic improvements in EMS ROSC
• Dramatic improvement in Survival to ED
• Significantly more admissions to ICUs

NO improvement in survival or good neurologic outcomes – only more prolonged ICU stays and costs

**Take Home #3**

“High-dose” epinephrine, of more than 1 mg per dose, significantly improves ROSC but not survival to discharge
How effective is Epinephrine in Cardiac Arrest?

The first major article to question the efficacy of epinephrine and other ACLS drugs in CPR
- 773 ED and IP patients, 5 Canadian hospitals
- 34.8% 1 hour survival
- All meds including epinephrine decreased survival

When age, gender, comorbid condition controlled for along with rhythm and cause of arrest:
“A significant association between unsuccessful resuscitation and the use of epinephrine”
(OR 0.08 95% CI .04-.14)

Do IV ACLS medications improve outcomes in cardiac arrest?
- 851 patients, Oslo Norway, 2003-2008
- 433 got “ACLS” but no IV meds
- No Epi, Atropine, Amio
- ACLS drugs improve ROSC, not survival

Conclusion
“Despite improved short term survival among patients randomized to receive IV access and drug administration, these nearly universal interventions were not associated with a statistically significant improvement in survival to hospital discharge”
Does Epinephrine improve survival in Cardiac Arrest when objectively studied?

• Double blind placebo controlled study
• 534 patients, OHCA, all bystander CPR
• Perth EMS in Western Australia; Epi 1 mg Q 3
• No other cardiac meds used
• Study size should have been 2,213 pts.

Does Epinephrine use have true benefits in CPR?

• Meta analysis, 14 RCTs, 12,246 patients
• Studies were:
  • Epi vs placebo (1) n = 534
  • Epi vs High does Epi (6) n = 6,174
  • Epi vs Vasopression (1) n = 336
  • Epi vs Epi + Vasopressin (6) n = 5,202

Results

• Epi vs placebo (1) n = 534 ↑ ROSC
  - No differences in survival or neuro outcome
• Epi vs High dose Epi (6) n = 6,174
  - No differences in survival or neuro outcome
• Epi vs Epi + Vasopressin (6) n = 5,202
  - No differences in ROSC, admit, survival or neuro
• Epi vs Vasopression (1) n = 336
  - No differences in ROSC, admit, survival or neuro

Take Home #4

There is not good objective evidence, in controlled studies, that epinephrine is more effective than placebo.
Maybe if epinephrine was given sooner it would work better

Does giving epinephrine sooner improve outcomes in out of hospital arrests?
- 686 pts, retrospective review, Royal Oak, Michigan
- 911 to Epi < 10 min vs > 10 min
- Evaluated rhythm and ROSC and survival to discharge
- Witnessed arrests: Early Epi increased ROSC by 3.2 X
- Early Epi did not improve survival to discharge

Survival and Time to Epi

Does time to epinephrine affect outcomes in non-VF-VT pediatric arrests?
- 1,558 pediatric patients
- Average age = 9 mos
- 31.3% overall survival rate
- 17.1% favorable neurologic status
- Matched rhythm and numerous variables

Results
- Longer time to epi = decreased ROSC
- Longer time to epi = worse survival
- ↓ time to epi = ↑ neurologic outcomes

Does timing of epinephrine affect neurologic outcome in cardiac arrest?
- 13,326 pts, retrospective Japanese database
- 2011-2014 data; divided pts into 2 groups
- 8 min from 911 to arrival and 8-16 min from 911
- Evaluated if epi given within 10 min of arrival
Early or Late Epi
Good Neuro Outcome at 1 Month

![Bar chart showing good neuro outcomes at 1 month for early vs late epinephrine administration.](chart.png)

- Early epinephrine improves ROSC and good neuro outcomes.
- Each minute delay decreases survival.
- Give early in arrest to optimize good outcome.

Take Home #5
Use epinephrine as soon as possible (until its effectiveness is proven or disproven)

Is earlier administration of epinephrine in VF more advantageous?

- 51% of patients received epi before 2nd shock
- 87% of both groups received 2nd defib
- Groups equal for total defibrillations (3)
- Early epi group received 3 mgs in average vs 1 mg in later dosing
- Similar TOR times (22 vs 21 mins)
Take Home #6

Wait for the second shock in VF/pVT to give epinephrine

There is no data to support giving epinephrine… Is there?

Does epinephrine affect survival and/or neurologic outcomes in Asystole and PEA?

- Japanese national database 2008-2012
- Used propensity matched pairs of patients
- 8,906 AS* paired and 7,451 pairs in PEA*
- Used time to epi, age and severity to pair
- Evaluated both survival and good neuro

*Only bystander witnessed arrests

Asystole Survival and Good Neuro Outcomes Epinephrine vs No Epinephrine

PEA Survival and Good Neuro Outcomes Epinephrine vs No Epinephrine
But…

• 1,556 patients from 2000 – 2012
• 1,134 (73%) received epinephrine
• 422 (27%) did not receive epinephrine
• Evaluated frequency of CPC 1 - 2 survival

Does prehospital epinephrine improve functional outcome post OOH cardiac arrest?

• 1,556 patients from 2000 – 2012
• 1,134 (73%) received epinephrine
• 422 (27%) did not receive epinephrine
• Evaluated frequency of CPC 1 - 2 survival

Epi vs No-Epi: CPC 1 - 2
Matched Pairs Evaluation

Study from Paris, France
All patients had ROSC
All were admitted
+ Epi patients: older, less witnessed
+ Epi patients: longer resuscitation, less VF/VT

Study compared 228 pairs of Epi vs non-Epi matched samples

Epi vs No-Epi
Additional Results

• Longer delay to epi = worse outcomes
• Negative effects of epi across subgroups
• Rhythm, TH, length of CPR, PCI
• The more the epi, the worse the outcome

Epi Dosing and Survival
CPC 1 - 2

• 1 Mg
• 2 - 5 Mgs
• > 5 Mgs

Epi Dosing and Survival
CPC 1 - 2

• 0.08
• 0.30
• 0.32
Take Home #7

Epinephrine’s role remains unclear.
The more you look, the more higher does of epinephrine look bad

Maybe we are just giving too much epinephrine?

Resuscitation 2014;85:350-8
Does dosing interval of epinephrine affect survival in CPR?
- 20,909 adult pts, 505 GWTG hospitals
- Looked at survival vs dosing interval
- Adjusted via multi-variate analysis
- Most common intervals were 4-5 and 5-6 min

<table>
<thead>
<tr>
<th>Epinephrine Dosing Intervals (min)</th>
<th>Adjusted Odds Ratio for Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3</td>
<td>1.00</td>
</tr>
<tr>
<td>3-4</td>
<td>1.00</td>
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<tr>
<td>4-5</td>
<td>1.41</td>
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<td>5-6</td>
<td>1.79</td>
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<td>6-7</td>
<td>2.17</td>
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Resuscitation 2017;117:18-23
Does spacing out epinephrine more than PALS/ACLS recommends affect pediatric CPR outcomes?
- 1,630 pediatric in-hospital arrests
- Intervals of 1-5, 5-8 min and 8-10 min evaluated
- Multi-variate analysis used to control co-morbidities
- Separately analyzed vasopressor use pre-arrest

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<tr>
<td>1-5</td>
<td>1.00</td>
</tr>
<tr>
<td>5-8</td>
<td>1.99</td>
</tr>
<tr>
<td>8-10</td>
<td>2.67</td>
</tr>
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</table>
Epinephrine Dosing Interval

- Although ACLS guideline say Q 3-5, it appears that spacing epinephrine doses out to up to 8-10 minutes may be optimal
- This is a violation of current guidelines
- No randomized study exists
- Give less not more

Take Home #8

Try to space your repeat doses of epinephrine by longer intervals not shorter ones

Maybe then, reduced dose epinephrine in cardiac arrest is the answer?

Could less than 1.0 mg be better dose of epinephrine?

- 2,255 pts from Seattle, 2008-2016
- 554 (24.6%) VF/VT; 1,701 (75.4%) AS/PEA
- Before and after type study
- VF/VT: 0.5 mg min 4, 8; AS/PEA: 0.5 mg Q 2 min
- Evaluated ROSC, Discharge, CPC 1-2

VF/VT Outcomes 0.5 mg vs 1.0 mg Epinephrine

<table>
<thead>
<tr>
<th></th>
<th>Std</th>
<th>Low</th>
<th>Std</th>
<th>Low</th>
<th>Std</th>
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</thead>
<tbody>
<tr>
<td>ROSC</td>
<td>12%</td>
<td>13%</td>
<td>13%</td>
<td>14%</td>
<td>12%</td>
<td>13%</td>
<td>12%</td>
<td>13%</td>
</tr>
<tr>
<td>Discharged</td>
<td>35%</td>
<td>36%</td>
<td>33%</td>
<td>34%</td>
<td>35%</td>
<td>37%</td>
<td>36%</td>
<td>38%</td>
</tr>
<tr>
<td>Good Neuro</td>
<td>32%</td>
<td>33%</td>
<td>32%</td>
<td>33%</td>
<td>32%</td>
<td>33%</td>
<td>32%</td>
<td>33%</td>
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AS / PEA Outcomes 0.5 mg vs 1.0 mg Epinephrine

<table>
<thead>
<tr>
<th></th>
<th>Std</th>
<th>Low</th>
<th>Std</th>
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<th>Std</th>
<th>Low</th>
<th>Std</th>
<th>Low</th>
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</thead>
<tbody>
<tr>
<td>ROSC</td>
<td>4.2%</td>
<td>4.7%</td>
<td>5.1%</td>
<td>5.6%</td>
<td>4.2%</td>
<td>4.7%</td>
<td>5.1%</td>
<td>5.6%</td>
</tr>
<tr>
<td>Discharged</td>
<td>22%</td>
<td>25%</td>
<td>29%</td>
<td>32%</td>
<td>22%</td>
<td>25%</td>
<td>29%</td>
<td>32%</td>
</tr>
<tr>
<td>Good Neuro</td>
<td>12%</td>
<td>15%</td>
<td>16%</td>
<td>19%</td>
<td>12%</td>
<td>15%</td>
<td>16%</td>
<td>19%</td>
</tr>
</tbody>
</table>
Low Dose Epinephrine
• Not a randomized trial
• Cross overs from either group
• 3.4 mg vs 2.6 mg in VF/VT; 3.5 mg vs 2.8 mg in AS/PEA

Reducing the dose of epinephrine in OOH cardiac arrests does not affect ROSC, hospital discharge frequency or neurologic outcomes in either shockable or non-shockable rhythms

Take Home #9
Reduced dose epinephrine offers no benefits

Final Take Home
Take Home #10
The case for or against epinephrine in CPR is embarrassingly not based on large randomized double-blind studies

Epinephrine Biases 2018
• The more epi, the more likely the patient will do worse – but the more epi, the longer the code
• High quality BCLS, later intubation, and selective application of ECLS seems more likely to save selected patients
• Earlier administration of epinephrine, not later, is well supported by multiple studies
• One dose after second shock for VF

Epinephrine in Cardiac Arrest Summary
• Use appears to decrease functional neurological status in survivors
• More epi = worse outcomes
• May increase ischemic-reperfusion and post-anoxic injury
• PCI and hypothermia do NOT attenuate Epi’s negative effects

Summary
Epi improves ROSC
Survival benefits unproven
Give early, not late
Give after second shock
Await London study